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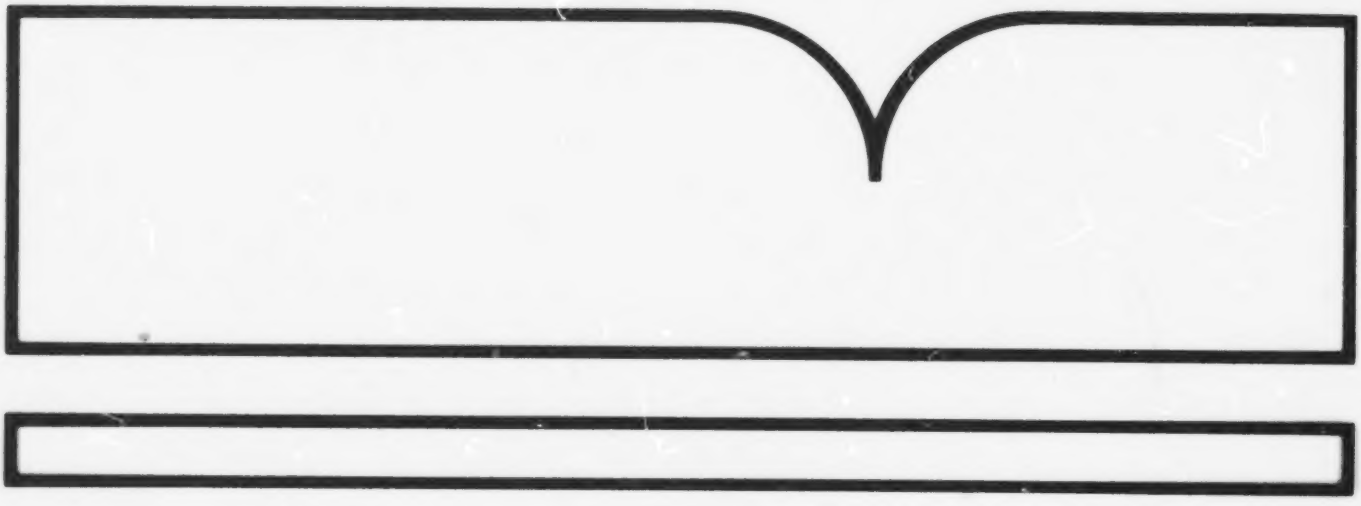

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ABSTRACT

Workers (N=229) from an Egyptian pesticide formulation plant were screened for signs of organophosphorus induced delayed polyneuropathy (OPIDP). Tests included lymphocyte neuropathy target esterase (LNTE), serum cholinesterase (ChE), tactile sensitivity (OPTACON), block design (BD) and Santa Ana Dexterity (SAD) tests. Workers from fertilizer (N=181) and textile (N=166) plants were tested as controls. A one-year follow-up evaluation of workers was also conducted. LNTE activity levels of pesticide formulators were significantly lower than levels of workers from other plants. Tactile thresholds varied significantly among plants (highest in pesticide plant) and for levels of education (inverse relationship) after controlling for age and LNTE activity. Tactile threshold increased linearly with age. BD and SAD scores did not vary with LNTE or among plants. Results suggest that tactile sensitivity testing may provide a useful method for early detection of peripheral neuropathy in workers exposed to pesticides.

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NEUROBEHAVIORAL ASSESSMENT OF WORKERS EXPOSED TO ORGANOPHOSPHORUS PESTICIDES*

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Organophosphorus (OP) compounds are widely used as pesticides, defoliants, flame retardants, emulsifiers, plasticizers and oil additives. Of considerable concern are more than a dozen outbreaks of human and animal neurotoxicity, resulting from OP chemical exposure, that have occurred during the past half century. Delayed neurotoxicity has been observed following human exposure to OP pesticides such as leptophos, methamidofos, trichlorfon and EPN (Metcalf, 1984). The cardinal features of organophosphorus-induced delayed polyneuropathy (OPIDP) are degeneration and secondary demyelination of peripheral and central nervous system axons occurring after a time delay of 8 to 14 days following exposure. Humans are the most susceptible species to OPIDP.

Recently, it was also found that fludarabine phosphate, an antitumor drug used in leukemia treatment, induced delayed neurotoxicity (21 to 43 days after starting treatment) in patients as manifested by cortical blindness and altered mental status (Warrell and Berman, 1986). Some patients experienced neurologic deterioration and died. Clinicopathologic evaluation suggested that widespread, severe demyelination was the cause of these reactions.

High level exposure to organophosphorus compounds can produce severe symptoms of delayed toxic neuropathy including numbness and tingling in the hands and feet, weakness of the lower limbs, balance problems, bilateral foot drop, and absence or reduction of ankle and knee jerk (Davis and Richardson, 1980; Xintaras and Burg, 1980). The effects of chronic occupational exposure to lower concentrations have not been studied extensively, although Metcalf and Holmes (1969), Xintaras et al. (1978), and Xintaras and Burg, (1980) have

examined a variety of neurobehavioral parameters in worker samples. Bowers, et al., (1964) exposed subjects experimentally to an OP compound similar to sarin. Results of these studies suggest that OP compounds produce mental confusion and impaired attention, memory, and visual function.

The early detection of OPIDP is of concern to public health agencies as increasing quantities of OP compounds are used in industry, agriculture and other sectors of the environment. Valid, sensitive, and reliable screening measures of biochemical and neurobehavioral symptoms of neurotoxicity are needed for this purpose. Althougn neurobehavioral tests appropriate for neurotoxicity field testing are available (Johnson et al, 1987), little evidence exists on the sensitivity to OPIDP of such tests.

Production workers in pesticide formulation plants are likely targets for OPIDP. Workers in underdeveloped countries such as Egypt are at risk due to the lack of occupational regulations and lax hygiene practices. In the present study workers from a pesticide formulation plant (N=229) at Kafr el Zayat in the Nile delta were selected for study with referent populations from a fertilizer plant (N=180) in Kafr el Zayat and a textile plant (N=167) in Alexandria. Evaluations included a health history, neurological symptom questionnaire, short neurological examination, blood draws for lymphocyte neuropathy target esterase (LNTE) and serum cholinesterase (ChE) measures, tactile testing with the Optacon, block design test and Santa Ana dexterity test.

METHODS

Selection of Workers

A subset of male production workers from three plants participated in this study. Workers at risk for OPIDN were selected from a pesticide formulation plant in Kafr el Zayat. At least four OP pesticides (EPN, leptophos, methamidofos, and trichlorfon) reported to induce OPIDP in humans (Metcalf, 1984) have been formulated at this plant. The total tonnage of organophosphorus pesticides formulated at the plant since it began operations in 1961 is shown in Table 1. Two referent populations were used--workers from a fertilizer plant also located in Kafr el Zayat and from a textile plant located in Alexandria. Fertilizer plant workers were similar in many respects to pesticide formulators. They shared the same food and water supplies, had the same cultural background, and were exposed to the same diseases. Fertilizer workers, however, were not exposed occupationally to pesticides. On the other hand, fertilizer plant workers were found to be exposed to two other toxic chemicals--sulfuric acid used to clean fertilizer vats and lead used to line the vats. No neurotoxic chemicals were found at the textile plant.

The total workforce was 600-700 workers at the pesticide plant, 800-900 workers at the fertilizer plant, and more than 1000 workers at the textile plant. The total number of workers participating from these plants were 229, 180 and 167, respectively. Workers scheduled for routine annual physical examinations during the period of the study were selected for testing. Pesticide and fertilizer plant workers were tested blindly at Kafr el Zayat

while textile workers were tested in Alexandria.

Demographic, Health History and Symptom Questionaire.

A questionnaire was administered to each worker (during the initial assessment only) to obtain demographic information (gender, age, education, employment history), workplace hygiene information, general health history, and specific neurological symptom history related to chemical exposure.

Neurobavioral Tests

On the basis of the existing literature on neurobehavioral symptoms of OP poisoning, a half-hour battery of pyschometric tests, tactile sensitivity assessment and neurological examination was designed and administered as described below.

Neurological Examination. Among the clinical symptoms of OP poisoning (Xintaras, et al 1978; Koller and Klawans, 1979; Davis and Richardson, 1980) are pupillary constriction (miosis) and blurred vision; muscular twitching, fasciculations and weakness; involuntary and intentional tremors; ataxia; impairment or loss of ankle, knee, and deep tendon reflexes; and impairments of memory and attention. A 10 minute neurological examination (Table 2) was used to evaluate these symptoms.

Tactile Sensitivity. Loss of tactile sensitivity is an early sign of peripheral neuropathy reported in cases of occupational exposure to organophosphates (Xintaras, et al., 1978; Koller and Klawans, 1979). Arezzo and Schaumburg (1980 and 1983) adapted the Optacon, a device which converts visual images to tactile sensations to enable blind persons to read, for neurotoxicity screening. The Optacon tactile stimulator is a rugged, lightweight (4lbs.) unit containing 144 miniature rods that vibrate continuously at 230 Hz. These rods protrude through a plastic plate on which the subject places the index finger of the nondominant hand (to minimize the effect of callouses or blisters). The height that the rods protrude above the surface of the plate and the intensity of vibration vary as a function of voltage. For neurotoxicity testing, the optical scanner is replaced by a digital voltmeter. Tactile sensitivity is measured as the voltage at which the subject detects a vibratory sensation in the index finger.

A two-alternative forced choice procedure was used to determine tactile threshold. Vibration intensity was initially set at a level of 6-8 volts, determined in a practice trial, that could be detected by everyone. The intensity was then reduced by 10% on successive trials until the first error occurred. The same voltage was then repeated. If a second error occurred, the voltage was increased once more. If a second incorrect choice was made, the voltage was increased by 10%, while if a correct choice was made the voltage was reduced by 10%. That is, after the first incorrect choice, each voltage level was repeated two or three times. Increases or decreases in voltage were then made based on two correct or incorrect choices. This

procedure was continued until a total of five errors occurred. Then the values of the five smallest correct choices and five incorrect choices were tabulated. Finally the lowest and highest values were cancelled and the remaining eight voltages were averaged to obtain the threshold value.

Block Design (BD) Test. BD is a subtest of the Wechsler Adult Intelligence Scale. This test has been used in neurotoxicity testing by the Finnish Institute of Occupational Health (Hanninen and Lindstrom, 1979), Valciukas and Lilis (1980), and NIOSH (Xintaras, et al., 1978). In the latter study, BD scores discriminated workers exposed to leptophos from non-exposed controls. This test provides a simple and objective measure of an individual's ability to perceive spatial relations and is very sensitive to brain injury (Matarazzo, 1972). Subjects were presented with a set of four or nine two-colored blocks and asked to reproduce nine patterns of increasing difficulty. Subjects were given five patterns containing four blocks (1 min. each) and 4 patterns containing 9 blocks (2 min. each).

Santa Ana Dexterity (SAD) Test. SAD is a simple and rapid test of hand-eye coordination and motor performance used by Hanninen and Lindstrom (1979), Valciukas and Lilis (1980), and NIOSH. SAD was also sensitive to leptophos exposure (Xintaras et al., 1978). The apparatus consisted of a board containing four rows of square holes. Each hole contained a peg with a circular head painted half-black and half-white. Subjects were asked to lift and rotate 180^{o} as many pegs as possible in 30 seconds. The test was performed twice with each hand and once with both hands.

Biochemical Tests

Venipuncture blood samples (2 x 5 ml) from each subject were drawn in evacuated heparinized or noncoated tubes. Lymphocytes were isolated from the first sample; serum was isolated from the second sample. Blood lymphocytes were isolated using the rapid one-step method of Boyum (1968). The protein contents of the lymphocyte preparations were determined by the Lowry method using bovine serum albumin as a standard (Lowry, et al., 1951). Blood samples (5 ml each) were centrifuged at 2000 x g for 10 minutes. The serum layer was drawn off and immediately used or stored at $-80^{o}C$ until used for ChE determinations. Lymphocyte-NTE activity was determined using the Johnson (1977) technique with slight modifications described elsewhere (Svendsgaard et al, 1988).

Statistical Hypothesis Testing

The hypotheses considered here are all cross-sectional. Some longitudinal hypotheses concerning the influence of the first year's data on the second year's data were tested, but are not reported here because there was no clear exposure relationship with neurobehavioral outcome. The main cross-sectional question was:

After adjusting for covariates (table 3) related to the neurobehavioral index (Optacon threshold, number of pegs twisted in 30 seconds in the Santa Ana Dexerity Test, or number of correct designs completed in the Block Design

Test), is there an association between the neurobehavioral index and pesticide exposure (ChE level NTE activity, worked at pesticide plant vs. worked at fertilizer plant, or interactions between pesticide plant work and selected covariates)?

Stepwise regression was used for statistical analysis. Data from the initial and follow-up evaluations were analyzed separately to confirm significant results that may arise by chance in only one year. Other steps to control the false positive rate due to multiple testing included designating certain tests to be confirmatory and others exploratory. The confirmatory tests were the association between the Optacon and LNTE, Santa Ana Dexerity Test and LNTE, and a neuropathy score based on certain items in the questionnaire and in the neurological exam. The questionnaire items detected very few workers responding positively to many questions concerning symptoms of peripheral neuropathy. The neurological exam detected no workers with obvious peripheral neuropathy. Thus, the peripheral neuropathy score can be considered insignificant. The workers may not have perceived the questionnaire items as pertaining to symptoms of peripheral neuropathy. For example, the few diabetics did not respond to these items on the questionnaire either.

Statistical testing was performed in the following manner. Covariates listed in Table 2 were entered in the regression equation until the largest F-statistic of the partial correlation of the remaining covariates was less than 1. Next, covariates were deleted from the regression equation until the smallest F of the variables in the equation was greater than 3.84. Next, it

was of interest to determine if the effect of the selected covariates varied between the two cities in which the plants were located. Crossproducts of selected covariates with city (textile plant) were tested for inclusion in the model to evaluate this question. Lastly, indices of pesticide exposure were considered for inclusion in the model in a one-at-a-time fashion. These indices are also listed in Table 3.

Since textile workers were not tested blindly, the question arose whether data from textile workers should be included with data from other workers in statistical analyses. Exclusion of data from textile workers simplifies comparisons and reduces the scope of inference . On the other hand, inclusion of data from textile workers substantially increases the sample size and improves the chance of detecting a disease-exposure relationship. It also increases the precision of estimating covariate effects and understanding the variability between two non-OP exposed populations. Therefore, textile workers were included in the analyses of objective endpoints (LNTE, ChE, tactile sensitivity, block design and Santa Ana dexterity), but were excluded from analyses of clinical measures (neurological examination) which are more open to subjective bias.

RESULTS

Demographic Data

Information concerning the age, years of employment, education, and smoking history of workers at each plant is shown in Table 4. There was a bimodal distribution of ages in the pesticide and fertilizer plants with a disproportionate number of young and old workers. Both younger and older workers in these plants were over-sampled in order to include adequate numbers of workers employed (or not employed) during leptophos formulation. A similar disparity occurred in years worked at plants, due in part to the length of time that the plants have been in operation. The textile plant has been in operation longer than the pesticide plant. The median education level of workers also varied somewhat among plants. A higher proportion of pesticide workers attended college (9.6%) than fertilizer (6.6%) or textile (4.8%) workers. The proportion of smokers was similar for the three plants.

Health History Questionaire Results.

Both pesticide and fertilizer workers expressed more general health problems than textile workers (back, hand/spinal injuries, kidney disease, anemia, arthritis, hypertension and work-related skin problems and hospitalizations.). Many questions concerned specific symptoms associated with organophosphorus pesticide exposure (Ecobichon and Joy, 1982). Percentages of workers from the three plants experiencing these symptoms are shown in Table 5. Both fertilizer and pesticide workers reported more

symptoms than textile workers. Pesticide workers expressed disproportionately more symptoms than workers from the fertilizer and textile plants on several items (numbness and pain in the hands, memory difficulty, visual blurring, stomach trouble, fainting).

Neurological Examination.

Consistent with results of the health history and symptom questionaires, workers in the pesticide and fertilizer plant were found to have more neurological impairment than textile workers on most tests. In several tests (hand coordination, involuntary tremor, and knee jerk) the differences between plants were quite dramatic, particularly in the initial examination (1985). Plant differences were similar in the follow-up examination (1986).

Since the workers from Alexandria and Kafr el Zayat were examined at different locations, testing of the textile workers was not done blindly. Therefore, conservative criteria were adopted for classifying neurological examination scores as "abnormal" and statistical comparisons were made only between pesticide and fertilizer workers. Except for the memory test, items were categorized either "normal" or "abnormal". Since OPIDP generally presents as a symmetrical disorder (Spencer and Schaumburg, 1976, Schaumburg et al., 1981 and 1983), scores were classified as "abnormal" only if the abnormality was observed bilaterally. Furthermore, scores were classified as "abnormal" only if the abnormality was observed both years.

Treated in this manner, examination scores were reduced to seven items.

Covariates were collapsed to two categories for analysis as follows: education level (secondary and college vs. others) and age (<40 vs #40). Proportions of workers in the two plants were compared on items where abnormalities occurred as defined above.

The proportion of workers with abnormal findings varied between plants for involuntary tremors and vibration sense only, as shown in Table 6. Pesticide workers scored significantly worse than fertilizer workers on these tests. Logistic regression analysis was used to test for an exposure effect (difference in abnormality rates between plants) while controlling for age and education. Only main effects of each factor were included because of instability in the estimates of the coefficients, and because the inclusion of interaction terms did not improve the fit of the model. The likelihood ratio test was used by refitting the model after removing the exposure variable. After adjusting for age and education, vibration rates varied significantly between plants (Chi-square = 46.3, $p<0.0001$). Involuntary tremor rates also varied between plants after adjusting for age and education. (Chi-squared = 4.55, p=05) LNTE and ChE

Mean LNTE and serum cholinesterase activity levels observed in workers from each plant in 1985 and 1986 are shown in Table 7. Significantly greater inhibition was found in pesticide than fertilizer or textile workers for both measures in 1985 and 1986. Enzyme analyses are described in detail elsewhere (Svendsgaard et. al., 1988).

Tactile Sensitivity.

An increase in Optacon voltage results in increased intensity of vibration of the stimulating rods. If higher Optacon voltages are required by a worker to perceive vibration, then that subject has increased vibratory threshold (or decreased tactile sensitivity) relative to other workers. Tactile sensitivity as indexed by log Optacon voltage varied with:

plant	sensitivity of pesticide workers was less than sensitivity of textile or fertilizer workers
age	decreased sensitivity with increasing age
hours worked per day	decreased sensitivity with longer workday (1985 only)
education	increased sensitivity in college-educated workers
LNTE	decreased sensitivity with increased inhibition (1986 only)
ChE	decreased sensitivity with increased inhibition (1986 only)
diabetes	decreased sensitivity in diabetics relative to others

Results of the multivariate regression analysis of Optacon voltage are shown in Table 8. The effects on tactile threshold of plant, education, and diabetes plotted as a function of age are illustrated in Figure 1. A significant interaction of age, plant and tactile sensitivity was found wherein sensitivity decreased with age more rapidly in pesticide workers than in other groups. This interactive effect appears in Figure 1 as a steeper slope for pesticide workers than other groups. Diabetics had the highest

tactile thresholds of any workers except the oldest pesticide workers.

Figure 2 shows the relationship of tactile sensitivity and percent change in LNTE inhibition (relative to median LNTE inhibition in referent textile workers) for 1986. Tactile thresholds increased slightly with greater inhibition of both LNTE and ChE, although the relationship reached significance only in the second year.

Santa Ana Dexterity and Block Design Scores.

SAD scores varied significantly with city (lower in Alexandria [textile workers] than in Kafr el Zayat [fertilizer or pesticide workers]), age (younger workers did better than older workers), and education (higher with increasing education level). SAD scores did not vary significantly with LNTE or ChE inhibition. Figure 3 illustrates the age effect. Block design scores increased significantly with higher education (Figure 4), but did not vary among plants, with ChE or with age.

DISCUSSION

LNTE as an Early Indicator of Delayed Neurotoxicity

A basic question examined in this study was the association between the inhibition of lymphocyte neuropathy target esterase and/or cholinesterase and neurological function as measured by medical history, neurological

examination, and several neurobehavioral measures. A longitudinal component was included to assess the progression of organophosphorus-induced delayed polyneuropathy (OPIDP). Results of the study provide limited support for the hypothesis of decreased neurological function as indexed by decreased tactile sensitivity in pesticide workers and with increasing LNTE inhibition. However, since no workers in the pesticide plant showed clearcut signs of OPIDP, the longitudinal component could not be used to assess the progression of disease.

Four pesticides (EPN, leptophos, methamidofos and trichlorfon) reported to induce OPIDP in humans (Metcalf, 1984) have been formulated in the Kafr el Zayat pesticide plant since the plant opened in 1961. Despite this fact, none of the pesticide workers examined was found to show obvious clinical signs of OPIDP. Several possible reasons may account for this finding. First, the formulation of trichlorfon was discontinued in 1970 and formulation of leptophos was terminated in 1975 (although leptophos continued to be stored at the plant until 1987). Workers adversely affected by exposure to these pesticides may have terminated employment at the plant years ago. Alternatively, workers experiencing subclinical effects during previous exposure could have recovered.

On the other hand, two other OP pesticides --- EPN and methamidofos -- were formulated quite recently -- until 1983 and 1986, respectively. Effects of exposure to these pesticides would be more likely to be detected. The relative delayed neurotoxicity of these pesticides in humans and the actual exposure levels in workers from Kafr el Zayat, however, are unknown.

Tactile Sensitivity as an Early Indicator of Neurotoxicity

The index of neurotoxicity that proved to be most sensitive to pesticide exposure was tactile sensitivity. Tactile thresholds, as measured by the Optacon voltage necessary to perceive vibratory sensation in the index finger of the nondominant hand, were higher in workers from the pesticide plant than in workers from the other two plants. Tactile thresholds also increased linearly with increased inhibition of LNTE and ChE, but only in the second year. Therefore, the latter observations must be interpreted cautiously. Results of the neurological examination provided further evidence of impaired tactile sensitivity. More pesticide than other workers were found to have abnormal vibratory sensation. In the symptom questionaire, numbness of the hands and feet was also reported more often by pesticide than other workers. Three different types of data obtained from workers in this study, therefore, indicate decreased tactile sensitivity in pesticide formulation workers compared to other workers.

The interactive effect of pesticide exposure, age and tactile threshold was of particular interest--i.e., tactile thresholds increased more abruptly with increasing age in pesticide workers than in other workers. This finding suggests that organophosphorus pesticide exposure may accelerate aging of the nervous system. Other toxicants have also been associated with accelerated aging. For instance, Cherry et al. (1983) reported that chronic solvent exposure produced increased deterioration of neurobehavioral function in older workers, an effect which they interpreted as accelerated aging.

Tactile sensitivity is a measure of the integrity of large diameter peripheral sensory nerves considered to be vulnerable to the effects of chemicals such as organophosphorus compounds which induce distal axonopathy (Spencer and Schaumburg, 1976). Case reports of OP poisoning frequently include symptoms of numbness in the feet and hands (Davis and Richardson, 1980). The present results are thus consistent with what is known about the mechanism of OPIDP and reported symptoms of accidental and intentional poisoning. Two subgroups of subjects provided evidence for the validity of the Optacon measure as an index of neurotoxicity. Peripheral neuropathy is a well-known sequela of diabetes (Schaumburg et al., 1983) and lead exposure in adults (USEPA, 1986). Workers diagnosed as having diabetes had the highest tactile thresholds of all worker groups. Tactile thresholds also increased linearly with blood lead (PbB) levels in fertilizer workers, particularly plumbers, in whom elevated PbB levels were observed. The Optacon has previously been found to be a useful index of neurotoxicity in workers exposed to acrylamide (Arezzo et al, 1983) and of toxic polyneuropathies in diabetics (Arezzo and Schaumburg, 1980; Arezzo et al, 1986). Results of the present study are consistent with previous reports that the Optacon is a useful device for neurotoxicity field testing of workers. The results also indicate the potential utility of the device in monitoring workers exposed to pesticides, lead and other neurotoxic chemicals.

Implications of Non-Blind Sampling

Failure to achieve blind sampling of workers from Alexandria and Kafr el Zayat limited the utility of textile workers as controls for pesticide workers and therefore limited the significance of comparing test results from textile workers with other workers. Since workers from the fertilizer and pesticide plants were examined blindly, some statistical analyses were limited to comparisons between these two plants. Comparisons between fertilizer and pesticide plants, however, are problematic because of possible contamination of food, water and air in Kafr el Zayat by chemicals from the pesticide plant and because fertilizer workers were routinely exposed to sulfruic acid which may have impaired tactile sensitivity in some of these workers. Both of these possible confounders, however, would reduce the probability of observing a significant pesticide-related difference between the plants--i.e., these factors would decrease the chance of type I errors, but increase the chance of type II errors.

Neurological Examination

In order to avoid the problem of non-blind evaluation of workers from Alexandria and Kafr el Zayat, statistical analysis of neurological examination data was limited to fertilizer and pesticide workers. Further stringent constraints were imposed on this analysis -- i.e., abnormal responses were required to occur bilaterally in both evaluations. Two out of seven items -- vibration sense and involuntary tremors -- still occurred more often in pesticide workers. The standard tuning fork method of determining vibration

sensitivity was used. The disproportionate incidence of abnormal vibratory sense in pesticide formulators provides concurrent validation of impaired tactile sensitivity as indexed by Optacon voltage. Involuntary tremors have also been noted previously as symptoms of OP pesticide poisoning (Davis and Richardson, 1980; Koller and Klawans, 1979).

Santa Ana Dexterity and Block Design Tests

Santa Ana Dexterity and Block Design test scores did not vary consistently with measures of cholinesterase or neurotoxic esterase inhibition, nor did these behavioral measures differ between the fertilizer and pesticide workers. Both tests did vary with the education level of workers--i.e., better scores were associated with better performance on both tests--suggesting that these tests were sensitive to other determinants of neurobehavioral function. The lack of association of SAD and BD scores with measures of exposure to OP compounds suggests that the neurobehavioral functions indexed by these tests were not affected by concentrations to which workers in the present study were exposed. SAD is a test of motor coordination while BD is a measure of higher level spatial processing. Only peripheral sensory nerves appear to have been affected by exposure to pesticides in these workers.

On the other hand, the limited nature of the neurobehavioral tests used in this study must be emphasized. This brief set of tests was not meant to provide a comprehensive assessment of neurobehavioral function. Computerized neurobehavioral batteries designed for occupational field testing are now

available (Baker et al., 1985) that would permit a more extensive evaluation of sensorimotor and cognitive functions affected by OP pesticide exposure. Therefore, the lack of association of SAD and BD scores with pesticide exposure measures should be interpreted cautiously.

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Table 1. Organophosphorus Pesticides Formulated at Plant

Pesticide	Years formulated	Total output (metric tons)
Trichlorfon	1961-1970	6,500
Leptophos	1968-1975	5,500
Methamidofos	1970-1986	5,300
EPN	1970-1983	1,500
Diazinon	1978-1986	6,500
Dimethoate	1978-1985	3,000
Malathion	1978-1985	3,000
Phenthoate	1986	500

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TABLE 2: NEUROLOGICAL EXAMINATION

1. Objects to be remenbered: Pencil, Book, School, Teacher, Ink.
2. Repeat the following numbers: 7 1 4 2 8 6 3
3. Coordination:

a - Rapid alternating movements with hand:

Right		Left	
N. Slow	V. Slow	N. Slow	V. Slow

b - Finger to nose rapid movements:

Right			Left		
1	2	3	1	2	3
normal	clumsy	post-pointing	normal	clumsy	post-pointing

c - Romberg's sign: + -

d - Gait:

1. High stepping
2. Slapping or unsteady
3. Scissoring. Stiff gait.
4. Ataxia, Reeling
5. Other abnormality
6. Normal

4. Tremors in hands at rest

Right			Left		
N.	Abn.		N.	Abn.	
f	c	o	f	c	o

5. Intention tremors:

Right		Left	
N.	Abn.	N.	Abn.

6.

Ankle Jerk		Knee Jerk		Babinski	
R	L	R	L	R	L
-	-	-	-	*	*
+	+	+	+		
-	-	-	-		
+	+	+	+		
++	++	++	++		
+++	+++	+++	+++		
++++	++++	++++	++++		

7. Sensation

	Pain sensation		Position sense				Vibration sense	
	R	L	R		L		R	L
Normal	---	---	N	Abn	N	Abn	---	---
Slightly dimin	---	---					---	---
Very dimin	---	---					---	---
Absent	---	---					---	---

8. Object Recall.....

Table 3. Summary of Dependent and Independent Variables

A. Dependent Variables

1. Lymphocyte Neuropathy Target Esterase (LNTE)
2. Serum Cholinesterase (ChE)
3. Tactile Sensitivity (Optacon Voltage)
4. Block Design (BD) Score
5. Santa Ana Dexterity (SAD) Score
6. Neurological Examination Scores

B. Independent Variables (Covariates)

1. Plant (Fertilizer, Pesticide, Textile)
2. Years Employed at Plant
3. Age of Worker
4. Education Level
5. Previous Work History
6. Hours Worked per Day
7. Use of Vibratory Tools
8. Smoking History
9. Health History
10. Data Collection Day

Table 4. Demographic Summary of Workers (Number of Workers per Category)

Demographic Variables	Textile (N=167)	Fertilizer (N=180)	Pesticide (N=229)
Age in years			
17-31	15	31	74
32-46	89	76	88
47-61	63	73	67
Years employed at plant			
1-11	25	68	117
12-26	87	63	96
27-46	55	49	16
Education level			
None	14	49	30
Elementary (1-3)	10	19	17
Elementary (4-7)	83	62	66
Primary (7-9)	22	13	43
Secondary (10-12)	30	25	51
College	8	12	22
Smokers			
Yes	91	98	121
No	76	82	107

Table 5. Worker Symptoms (percentage)

	TEXTILE	FERTILIZER	PESTICIDE
Muscle Weakness	25.5	35.4	43.2
Numbness: Legs, Feet	6.6	22.8	38.8
Pain in Both Legs	6.0	19.4	33.0
Numbness: Hands	3.6	5.0	34.4
Pain in Both Hands	2.4	4.3	29.5
Memory Difficulty	16.2	16.1	28.8
Unusual Tactile Sens.	9.0	5.0	5.7
Frequent Headaches	21.0	29.1	35.1
Difficulty Sleeping	18.7	15.6	23.6
Coordination Problems	18.7	19.4	20.5
Tension/Nervousness	30.5	31.1	35.1
Depression	22.2	23.9	28.1
Irritability	25.8	21.9	30.1
Frequent Nightmares	2.4	7.3	9.6
Visual Blurring	21.0	24.0	30.1
Slurred Speech	3.0	1.1	4.8
Difficulty Swallowing	3.6	5.0	5.7
Stomach Trouble	8.4	12.8	20.7
Loss of Balance	13.2	27.8	29.0
Dizzy Spells	10.8	16.7	19.7
Fainting	3.0	2.2	3.5
Frequently Tired	22.8	27.9	37.3
Unexpected Sweating	11.4	27.8	32.2
Unexpected Weight Loss	6.0	8.9	12.2
Frequent Diarrhea	1.8	5.0	9.2

Table 6. Percentage of Workers in Fertilizer and Pesticide Plants with Abnormal Vibration Sense and Involuntary Tremors

Education	Age	Fertilizer	Pesticide
(a) Vibration Sense (Rate of Abnormal Responses)			
Less than Secondary	<40	14.0% (7/50)	43.2% (35/81)
Less than Secondary	≥40	22.0% (17/77)	65.6% (40/61)
Secondary or College	<40	10.5% (2/19)	25.6% (11/43)
Secondary or College	≥40	0.0% (0/8)	42.1% (8/19)
(b) Involuntary Tremors			
Less than Secondary	<40	4% (2/50)	7.4% (6/81)
Less than Secondary	≥40	3.9% (3/77)	13.1% (8/61)
Secondary or College	≤40	0.0% (0/19)	11.6% (5/43)
Secondary or College	≥40	12.5% (1/8)	0.0% (0/19)

Table 7. Biochemical Means, Medians, and Standard Deviations by Plant

LNTE (n moles/hr/mg protein)

		Fertilizer	Pesticide	Textile
1985	N	177	227	167
	Average	458	370	472
	Median	445	358	458
	S.D.	128	121	106
1986	N	147	194	110
	Average	419	356	502
	Median	403	315	488
	S.D.	132	129	115

Serum Cholinesterase (mU)

		Fertilizer	Pesticide	Textile
1985	N	178	228	167
	Average	2353	2172	2301
	Median	2451	2359	2359
	S.D.	383	508	363
1986	N	147	202	110
	Average	2305	2098	2376
	Median	2299	2064	2369
	S.D.	531	568	402

Table 8. Analysis of Log Optacon Voltage

Independent Variables	F-statistic			
	Year of data collection			
Description	1985 N=571		1986 N=465	
A. Results of selecting covariates				
data collection day		18.96 (-)*		15.91 (+)
Textile worker		63.80 (-)		13.50 (-)
age		18.04 (+)		9.39 (+)
attended college		11.08 (-)		NS
worked at other chemical plant		6.69 (-)		NS
reported he had diabetes		5.86 (+)		NS
hours worked per day		30.11 (+)		NS
Total covariate R squared	37.4%		5.5%	
B. Exposure variables examined				
pesticide worker	**		**	
age x pesticide worker	1.3	11.45 (+)	1.3	6.82 (+)
Hourswork x pesticide worker	1.7	15.88 (+)	2.0	10.27 (+)
	1.3	11.06 (+)	***	***
Inhibition of LNTE				
greater than 25	NS	0.18	1.2	5.62 (+)
greater than 50	NS	0.02	0.9	4.15 (+)
Inhibition of cholinesterase	NS	0.24	0.8	3.39 (+)
greater than 25	NS	0.18	1.9	5.08 (+)
greater than 50	NS	0.14	1.6	3.61 (+)
	NS	0.28	1.7	3.70 (+)

* (+) and (-) indicate the sign of the regression coefficient when the variable is included in the model and it is significant at 0.05 level one-sided.

** Increase in percent R-squared over total covariate R-squared when each of the below exposure related variables is included one-at-a time into the regression model.

*** Not tested since the variable "hours worked per day" was not significant in 1986 analysis.

FIGURE LEGENDS

Figure 1. Effects of age, plant, diabetes and education on tactile sensitivity, controlling for sampling day and 8-hr workday. (C) college graduates. (D) self-reported diabetic. Tactile sensitivity measured in units of log optacon voltage, 1985 assessment.

Figure 2. Tactile sensitivity (log optacon voltage) as a function of LNTE inhibition relative to the median LNTE inhibition in textile workers. Vertical bars represent standard error.

Figure 3. Santa Ana Dexterity scores as a function of age. Vertical bars indicate +/- one standard deviation.

Figure 4. Block Design scores of pesticide workers as a function of education. Vertical bars represent +/- one standard deviation.

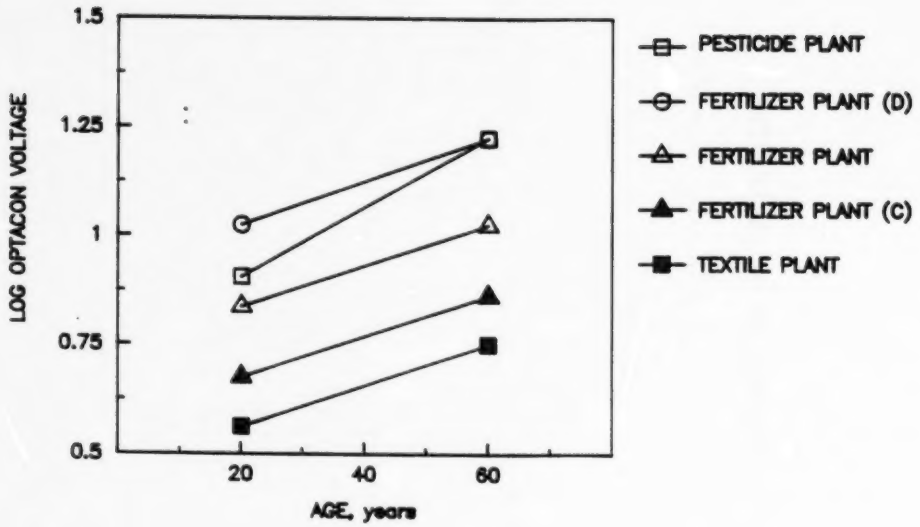
LOG OPTACON VOLTAGE
1.5
1.25
1
0.75
0.5
20
40
60
AGE, years
PESTICIDE PLANT
FERTILIZER PLANT (D)
FERTILIZER PLANT
FERTILIZER PLANT (C)
TEXTILE PLANT

FIG. 1

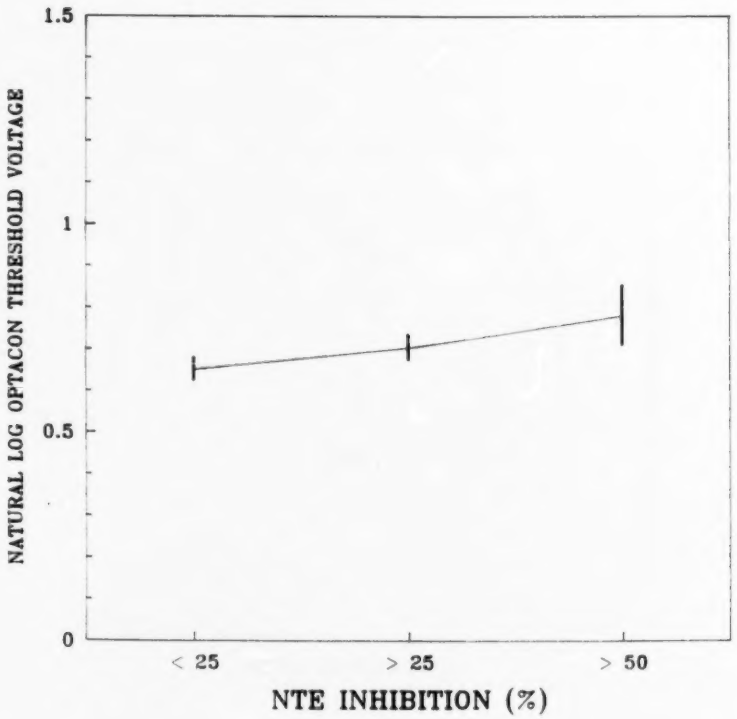
NATURAL LOG OPTACON THRESHOLD VOLTAGE
1.5
1
0.5
0
< 25
> 25
> 50
NTE INHIBITION (%)

FIG. 2

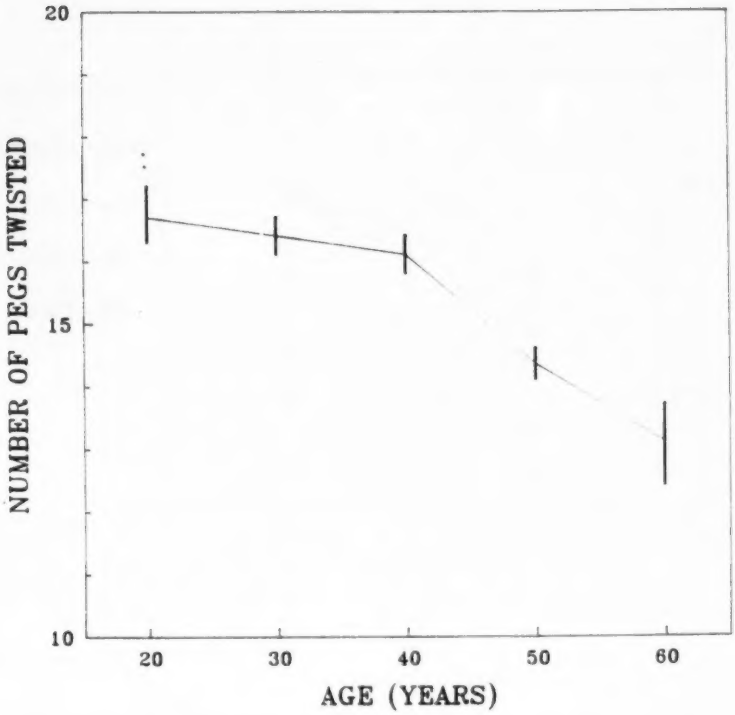
NUMBER OF PEGS TWISTED
20
15
10
20
30
40
50
60
AGE (YEARS)

FIG. 3

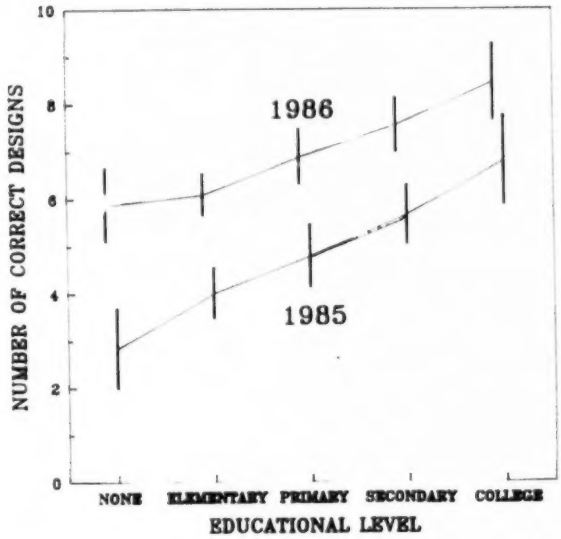
NUMBER OF CORRECT DESIGNS
10
8
6
4
2
0
1986
1985
NONE
ELEMENTARY
PRIMARY
SECONDARY
COLLEGE
EDUCATIONAL LEVEL

FIG. 4